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EXAMINER	
SPECTOR,L	
ART UNIT	**PAPER NUMBER**
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18N2/1114

DARYL B WINTER
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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474..
6. ☒ Notice To Comply.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-27 are pending in the application.
   Of the above, claims 1-10, 22-27 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 11-21 are rejected.
5. ☐ Claims _____ are objected to.
6. ☒ Claims 1-27 are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

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EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

Part III: Detailed Office Action

Restriction Requirement:

Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1-8, 24, 26 and 27, drawn to MPL ligand polypeptides and compositions thereof, classified in Class 530, subclass 351.

II. Claims 9 and 10, drawn to antibodies and hybridoma cells, classified in Class 530, subclass 387.1 and Class 435, subclass 240.27.

III. Claims 11-21, drawn to nucleic acids, vector and host cells, classified in Class 536, subclass 23.5 and Class 435, subclasses 71.1, 240.1 and 320.1 for example.

IV. Claims 22 and 23, drawn to method of hybridization and amplification, classified in Class 435, subclass 6.

V. Claims 25, drawn to treatment of thrombocytopenia using MPL ligand, classified in Class 514, subclass 12.

The inventions are distinct, each from the other because of the following reasons:

The nucleic acids of Invention III are related to the protein of Invention I by virtue of encoding same. The DNA molecule has utility for the recombinant production of the protein. Although the DNA molecule and protein are related since the DNA encodes the specifically claimed protein, they are distinct inventions because they are physically and functionally distinct chemical entities, and the protein product can be made by another and materially different process, such as by synthetic peptide synthesis or purification from the natural source. Further, the DNA may be used for processes other than the production of the protein, such as nucleic acid hybridization assay.

The proteins of Invention I are related to the antibodies of Invention II by virtue of being the cognate antigen, necessary for the production of the antibodies. Although the protein and antibody are related due to the necessary stearic complementarity of the two, they are distinct inventions because they are physically and functionally distinct chemical entities, and because the protein can be used another and materially different process from the use for production of

the antibody, such as in a pharmaceutical composition in its own right, or to assay or purify the cognate receptor of the protein (as the protein is itself a ligand), or in assays for the identification of agonists or antagonists of the receptor protein.

The proteins and compositions are distinct and unrelated to the methods of Invention IV, wherein each is not required for the other, and the proteins cannot be either used nor produced by the methods.

Inventions I and V are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case the product may be used as an antigen for the production of the antibodies of Invention II.

The compositions of Inventions II and III are physically and functionally distinct products which are capable of separate manufacture and use, and which have distinct biological and chemical properties.

The antibodies and cells of Invention II are patentably distinct from the methods of each of Inventions IV and V, wherein the antibodies and cells may be neither produced by nor used in either of the methods.

The nucleic acids of Invention III and methods of Invention IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case the product may be used for the recombinant production of the protein of Invention I.

The products of Invention III and methods of Invention V are patentably distinct, wherein the products may be neither made by nor used in the methods.

The methods of Inventions IV and V are independent and distinct processes of using

different products, and involve separate process steps and results.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with Darryl Winter on September 13, 1995 a provisional election was made with traverse to prosecute the invention of group III, claims 11-21. Affirmation of this election must be made by applicant in responding to this Office action. Claims 1-10 and 22-27 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

Formal Matters:

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The disclosure is objected to because of the following informalities; Appropriate correction is required for each listed item:

-The status of any and all applications to which cross reference is made should be updated as appropriate.

-At page 71 line 18, the phrase "was had" appears and has unclear meaning.

-At page 71, line 33 the word "performed" is misspelled.

-The discussion of sequences at page 72 should refer to the appropriate sequence identifiers (SEQ ID NO:) as well as or instead of to Figure 7.

-The limitation in claim 15 that the claimed DNA encode SEQ ID NO:2 is redundant, as such limitation is already found in the independent claim (3) upon which the claim indirectly depends.

-The punctuation in claim 20 is misplaced; the period should appear at the *end* of the claim.

37 CFR 1.822(j) provides that nucleotide sequences shall only be represented by a single strand, in the 5' to 3' direction, from left to right. That is, double stranded nucleotides shall not be represented in the "Sequence Listing." A double stranded nucleotide may be represented as two single stranded nucleotides, and any relationship between the two may be shown in the drawings. It is noted that SEQ ID NOs:5, 13, 15 and 18 are is reversed polarity; that is, they depict the complementary strands to SEQ ID NOs:4 (e.g. the "2nd" strand of Figure 7), 12, 14 and 17 in 3' -> 5' orientation, rather than giving the sequences in 5' -> 3' orientation as required by 37 CFR 1.822(j). The sequence listing and CRF should be amended to reflect the proper polarity as required by 37 CRF 1.822(j). Applicants are reminded that, in submitting an amended CRF diskette, *the entire set of sequences* should be resubmitted (i.e. send a complete sequence listing on a single diskette) to avoid confusion. Please see the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

37 C.F.R.§1.821(d) reads as follows:

> (d) Where the description or claims of a patent application discuss a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the assigned identifier, in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

The claims and/or specification are not in full compliance with 37 C.F.R.§1.821(d), and should be amended to refer to the appropriate sequence identifier(s) (SEQ ID NO:). For example, see claim 13. Correction is required.

Double Patenting Rejections:

It is noted that this application is a member of a large family of applications, including serial numbers 08/185607, 08/196689, 08/223263, 08/249376, 08/348657, 08/374540 and 08/425016, as well as the divisional applications derived from each of the aforementioned cases and the instant case. There are myriad possible provisional statutory and obviousness type double patenting rejections which might be made between the claims of the instant application and its various copending applications. It is beyond the resources of the PTO to establish each and every possible double-patenting rejection which might be made among the pending claims. 37 C.F.R. § 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See M.P.E.P. § 822. The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 11-21 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 11-13 and 16-21 of copending application Serial No. 08/196689 and over claims 20-31 of copending application Serial No.08/249376. Although the conflicting claims are not identical, they are not patentably distinct from each other because all the claims in question are drawn to nucleic acids, vectors, and host cells which encode mpl ligand, and recombinant production of mpl ligand. The claims vary only in specific recitations of amino acid sequence portions encoded by the claimed nucleic acids, and/or in the scope of the claims, in that some claims are limited to nucleic acids encoding mpl ligand from particular biological species, whereas other claims are more generic, being drawn to nucleic acids encoding mpl ligands without reference to biological species. However, the claims of each

application are considered to be obvious over the others because the sequence limitations are considered to be inherent properties of the disclosed nucleic acids, and further, because having obtained one nucleic acid sequence encoding an mpl ligand, it would have been obvious to obtain nucleic acids encoding both mpl ligands from other mammalian species, and to obtain allelic variants of such in view of the biological importance of the encoded protein. Thus, in the event that the claim limitations actually describe different species, such species are considered, in the express absence of evidence to the contrary, to be *prima facie* obvious over one another.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention.

The current specification as filed fails to adequately describe what is meant by "*mpl* ligand polypeptide." There is adequate definition in the specification of the term "*mpl* ligand" (see page 18), however the Examiner can find no definition of the term "*mpl* ligand polypeptide." The word polypeptide is used variously in the art to refer to any protein, or fragment of any protein which consists of more than a few amino acid residues. The absence of any indication in the specification as to what applicants intend the term "*mpl* ligand polypeptide" to designate (that is, is this a full-length *mpl* ligand, or do applicants intend to also claim nucleic acids encoding any fragment thereof which may or may not be an *mpl* ligand in and of itself) results in a failure of the current specification as filed to provide an adequate written description of the invention as it is currently claimed.

The specification presents a confusing account of which clone is expected to represent the claimed nucleic acid encoding human mpl ligand. At page 71, the specification clearly states that

"One of these clones, 35 U.S.C. §16, was had the correct sequenced based on its restriction profile as compared to clone #4 described below." This statement would seem to indicate that clone 16 is the desired clone, and that clone 4 is *not* thought to be the correct human mpl ligand clone. However, Example VII, starting at page 72, presents a discussion of clone 4 as though it *is* presumed to be the desired clone. Therefore, it is not clear from the specification which clone or clones is thought to represent the human mpl ligand-encoding sequence. Further, as the specification seems to indicate that the majority of obtained clones were *not* thought to represent the desired sequence, it is not clear what the desired and claimed sequence *is*, nor how one would distinguish it from the other, non-desired sequences. Finally, it is noted that, as the disclosed clones are not described in such a manner as to enable the skilled artisan to make them nor was an appropriate biological deposit of such made in accordance with 37 C.F.R. §1.801-1.809, that none of the disclosed clones can be relied upon to establish enablement of the claimed invention, with the exception that the particular sequence of Figure 7, which itself is clearly stated to represent only a portion of the undescribed complete mpl ligand protein, is clearly adequately described and thus is not enabled.

The specification as filed does not present enablement which is commensurate in scope with the claims. It is noted that the specification discloses isolation of a cDNA clone from a human cDNA library, which clone has a partial sequence that seems to encode the human homologue of porcine mpl ligand, but that the specification does not identify the complete coding sequence, the complete protein encoded thereby, nor is there any characterization of the encoded protein with regard to structure-function relationship. The claims are variously drawn to nucleic acids which (a) encode any isolated human mpl ligand polypeptide comprising at the N-terminus SEQ ID NO:2 (e.g. claim 11 and its dependents), (b) encode any human mpl ligand meeting the limitations of claim 2 (e.g. SEQ ID NO:2, stimulation of *mpl*-bearing IL-3 dependent Ba/F3 cells, glycoprotein, acid stability, e.g. claim 12) (c) any nucleic acid comprising nucleotides 119-196 of Figure 7 (e.g. claim 13) or (d)any nucleic acid which either encodes any mpl ligand, hybridizes to any such nucleic acid, or which is a variant of either of the aforementioned and which encodes

a polypeptide possessing "a biological property" or any naturally occurring mpl polypeptide.

Enablement is not commensurate in scope with claims as discussed above because the claims read on any nucleic acid which encodes full-length naturally occurring mpl ligand (ML), as well as various unspecified and non-described truncations, deletions and alterations of such a sequence, as well as innumerable proteins which might be only distantly related or unrelated, which happen to meet the limitations. The examples in the specification do not clearly establish what constitutes human ML, as such has not been fully described. There has been no description of which portions of the encoded protein would reasonably be expected to be necessary and sufficient to meet the limitations, nor any disclosure of how the encoding sequence might be alterable while still meeting the limitations of the claims. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, catalysis and in providing the correct three-dimensional spatial orientation of binding and catalytic sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions. However, applicants have provided little or no guidance beyond the mere presentation of *partial* sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Such a definition might also read on previously characterized proteins, or alternatively, might include proteins with additional functions or activities neither envisioned nor enabled by applicants in the current invention. See Ex parte Forman, 230 U.S.P.Q. 546 (BPAI 1986) with regard to the issue raised above.

The Examiner notes that the description of nucleic acids via a single biological function (in this case that of encoding proteins with a particular N-terminal sequence and/or biological characteristics) is similar to the situation in *Ex parte Maizel* (27 USPQ2d 1662 at 1665) in which it was found that:

> Appellants have not chosen to claim the DNA by what it is but, rather, by what it does, i.e., encoding either a protein exhibiting certain characteristics, *or* a biologically functional equivalent thereof. Appellants' claims might be analogized to a single means claim of the type disparaged by the Court of Customs and Patent Appeals in *In re Hyatt,* 708F.2d 712, 218 USPQ 195 (Fed. Cir. 1983). The problem with the phrase "biologically functional equivalent thereof" is that it covers any conceivable means, i.e., cell or DNA, which achieves the stated biological result while the specification discloses, at most, only a specific DNA segment known to the inventor. Clearly the disclosure is not commensurate in scope with the claims."

In the current instance, the claims do not positively identify the nucleic acids which are the basis for the currently claimed invention, but rather define such in terms of a partial sequence without regard to function, or the function of encoding a protein with particular, ill-defined properties. Therefore, the currently pending claims are analogous to the claims in *Maizel.*

Enablement is also not commensurate in scope with claims to nucleic acids which hybridize under stringent conditions to the particularly disclosed nucleic acids, which may or may not themselves encode any protein, much less one with ML biological activity. The examples provided in the specification do not provide a representative number of different DNA sequences for the entire scope of the claims that would enable all of the above discussed DNA sequences with assurances that they possess or encode proteins having the desired activity, nor does the specification teach how to use nucleic acids which do not encode such proteins. The general disclosures of (for example) what conservative substitutions are do not serve as sufficient guidance to enable the breadth of the Claims for the various DNA sequences claimed. See Ex parte Forman, 230 USPQ 546. Since the first paragraph of the statute under 35 USC 112 requires that there must be an enabling disclosure to support the breadth of the Claims, a review of the

specification confirms that the scope of the various DNA sequences that are discussed above have not been enabled. In the absence of sufficient guidance, it would require undue experimentation to enable all of the sequences that are encompassed by the Claims.

Not only would it be time consuming, it would also be unpredictable to prepare all of these DNA sequences that have the activities discussed with the assurance that they will hybridize under the specified conditions.

The language of "DNA that hybridizes under stringent conditions to..." covers virtually all future mutations or modifications of the DNA sequences, because the claimed sequences would be expected to hybridize to all future sequences, even those not contemplated by the Applicants at the time the Invention was made. In view of the fact that the disclosed ML is part of a multi-gene family (as evidenced by its relatedness to EPO), it would be expected that DNA encoding other members of the family (and possibly including EPO) would be capable of hybridizing to the disclosed sequences.

Initially, many Inventors intended for the term "hybridize" to mean homologous DNA obtained from other species. Now, Inventors and others seek to extend the meaning to encompass minor variations and such as well. The Examiners position is consistent with the Office policy, because the Office's position has been and still is that broad claims must necessarily have broad-based enabling support and this has also been the position of several case law decisions. Further, the Examiners rejection of the Claims for non-enablement is supported by statutory requirements an is consistent with long standing case law for such issues such as In re Fisher (166 USPQ 18) and even more recent case law that are particularly on point with this rejection such as Amgen v. Chugai (18 USPQ 2d 1017).

Claims 11-21 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 11-13 and 15-21 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention.

Claims 11 and 12 (and their dependent claims) are indefinite for depending from non-elected claims. The claims should be amended to incorporate the relevant limitations of the claims from which they depend.

Claim 13 is indefinite for reciting "SEQ ID NO:*". The appropriate sequence identifier should be stated.

Claim 19 is incomplete for failing to recite a step for isolation or recovery of the produced protein.

Prior Art:

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Methia (Blood 82:1395, 1993) suggests that *mpl* is a cytokine receptor for a thrombopoietic cytokine and suggests using the receptor to clone the ligand. Note the ultimate paragraph (Page 1400) which indicates that it was not known whether *mpl* was a single- or multi-chain receptor.

Skoda (EMBO 12:2645, 1993) indicates that as of 1993 it was still unknown whether *mpl* had a ligand binding domain, or alternatively required a heterologous protein to form or supply the ligand binding domain (see paragraph bridging columns of page 2651).

McDonald et al. (Exp. Hematol. 16:201) disclose that TSF (another name for TPO) had been purified to homogeneity from HEK cell culture medium (see page 202, first column). The final paragraph of the paper suggests cloning and recombinantly producing thrombopoietin.

McDonald et al. (J. Lab. Clin. Med. 106:162) discloses the purification to homogeneity of thrombopoietin from HEK cell culture medium.

Advisory Information:

The claims are free of the cited prior art. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 8:00 A.M. to 4:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ms. Garnette D. Draper, can be reached at (703)308-4232.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The Art Unit 1812 Fax Center number is (703) 308-0294. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the Examiner at the telephone number above when a fax is being transmitted.

Lorraine Spector, Ph.D.
Patent Examiner

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11/2/95

Application No. 09/378,650

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the following reason(s):

☐ 1. This application clearly fails to comply with the requirements of 37 CFR 1.821 - 1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☑ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).

☑ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached marked-up copy of the "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).

☐ 7. Other: _____

Applicant must provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing"

☑ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification

☑ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)

For questions regarding compliance with these requirements, please contact:

For Rules Interpretation, call (703) 308-1123
For CRF submission help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

Please return a copy of this notice with your response.